REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow. As correctly indicated in the Office Action Summary, claims 21-39 and 41-43 are pending.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 21-32 stand rejected under 35 U.S.C. § 102 (b) as purportedly anticipated by Southern *et al.* (WO 95/04160).

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." Jamesbury Corp. v. Litton Industrial Products, Inc. 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). The cited reference does not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below.

The Office Action appears to indicated that the phrase "same reaction zone" means the place on the template molecule where ligation takes place. However, Applicants note that this is not the intended meaning. Applicants submit that the skilled artisan, based on what is disclosed in the specification and known in the art, would give the words "reaction" and "zone" their common meaning and understand that a reaction zone refers to a container or region where the templates are located in which the sequencing reaction takes place. More specifically, the definition of "reaction zone" refers to a region in which the tags are detected from an individual sequencing reaction. The present specification, page 7, lines 16-18, supports this

assertion, disclosing the construction of reaction zone as a region where sequencing reaction takes place. The specification states "the invention provides a method for analysing heterogenous sub-populations of nucleic acids without spatially resolving them" [emphasis added]. The phrase "without spatially resolving them",indicates that the templates are present in the same container or region and are sequenced without the need for separation.

In contrast, Southern *et al.* disclose sequencing multiple templates. *See* page 17, lines 7-23. The individual templates are immobilized on an array of pins. Therefore, Southern *et al.* disclose that the templates must be spatially resolved. Page 17, line 24 to page 18, line 5 of Southern *et al.* discloses that different targets may be immobilized at individual spaced locations of a support, indicating that the templates must be spatially resolved. In contrast the presently claimed invention permits several templates to be present in the same area (for example on the same pin in the array of pins disclosed in Southern *et al.*). In the approach disclosed in Southern *et al.*, each pin would release one tag per cycle of sequencing corresponding to the sequence of the template on the pin. In the present application, each pin would release as many tags as there are templates on the pin during each cycle of sequencing. The present application enables all the tags to be detected simultaneously, whereas Southern *et al.* teach detecting each tag separately. The concept of analyzing multiple templates that are not spatially resolved is not disclosed by Southern *et al.*

The Office Action asserts that the subject matter of part (a) of claim 21 is disclosed in Figure 5, Example 16b and claims 16a and 16b of Southern *et al.*

Figure 5 illustrates a single target nucleic acid. Therefore, this Figure does not disclose a heterogenous population of single stranded DNAs, each of which are present in a unique amount, nor does it anticipate part (a) of claim 21. Example 16b of Southern *et al.* merely discloses a single template. Furthermore, claims 16a and 16b do not disclose, directly and unambiguously, sequencing more than one target nucleic acid. Thus, the passages and figures cited by the Examiner do not disclose the subject matter of part (a) of claim 21.

The Office Action further asserts that step (b) of claim 21 is disclosed in Figures 1-5, claim 16 (parts a-d) and claim 20 (parts a-d) of Southern *et al.* Purportedly, Figures 4 and 5 illustrate bybridising the templates with an oligonucleotide pool, and claim 16 (parts a-d) and claim 20 (parts a-d) disclose incubating the hybrid with a library comprising 4th reagents. Although the Figures of Southern *et al.* disclose the feature of contacting a DNA with an array of hybridisation probes, they do not disclose that the hybridisation probes in the array are incapable of ligation to each other. Part (b) of claim 21 is directed to contacting the DNA templates with an array of hybridisation probes, wherein the sequences of each probe are "incapable of ligation to each other". In addition, the claims and Figures cited by the Examiner as reading on the claimed invention disclose that the step of hybridisation is distinct from the ligation step. Part (b) of claim 21 requires that hybridisation to be carried out in the presence of a ligase.

The Office Action indicates that part (e) of claim 21 is disclosed in Example 19, Figures 3b, 4 and 5, and in claims 16 (part f) and 20 (part f) of Southern *et al.* Example 19 indicates that a compound produces a large peak at a mass of 304 Da.

However, it does not disclose that the quantity of each label is recorded. Figures 3b, 4 and 5 indicate that a sequence can be deduced by reading the code of the tag moiety. These figures do not indicate that the quantity of the entire tag is determined. Claims 16(f) and claim 20(f) of Southern *et al.* disclose the recovery and the analysis of the tag moiety. The claims of Southern *et al.* do not disclose that the quantity of the label is determined. Therefore, the passages and figures in Southern *et al.* that are cited by the Office Action do not disclose the subject matter of part (e) of claim 21.

Southern *et al.* do not disclose the subject matter of parts (a), (b) and (e) of claim 21. Southern *et al.* does not disclose combining a heterogeneous DNA population in a single reaction zone, that the single stranded DNAs are present in a unique amount, that the hybridisation probes are incapable of ligation together, that the hybridisation and ligation steps lake place simultaneously, nor does it disclose that the quantity of each label is recorded. Southern *et al.* does not disclose sequencing multiple templates in the same reaction zone using the points discussed above. Thus, claim 21 is novel over the disclosure of Southern *et al.*

Therefore, Applicants respectfully request the withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 102(a)

Claims 21-25 and 27-32 stand rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Macevicz *et al.* (WO 96/33205). The cited reference does not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below.

The Office Action asserts that claims 21 to 25 and claims 27 to 32 are anticipated by Macevicz *et al.* In particular, the Office Action states that part (a) of claim 21 is disclosed in Figure 1, and on page 10, line 16 to page 11, line 23 of Macevicz *et al.* Applicants submit that Figure 1 does not disclose a heterogeneous population of single stranded DNAs, each of which is present in a unique amount. Rather, it discloses aliquots of the same single stranded DNA. This interpretation is supported by page 4. lines I to 2 of the description of Macevicz *et al.*, which states that "a plurality of different initialising oligonucleotides is provided for separate samples of the template". In addition, page 10, line 16 to page 1, line 23 of Macevicz *et al.* do not disclose a heterogeneous population of single stranded DNAs, each of which is present in a unique amount.

The Office Action indicates that Figures 1 to 4 and claim 13 of Macevicz *et al.* disclose the subject matter of part (b) of instant claim 21. Step (c) and step (d) of claim 13 of Macevicz *et al.* disclose annealing an oligonucleotide probe (which may be a mixture of oligonucleotides of all possible sequences of a predetermined length) to the template followed by ligating the oligonucleotide probe to the primer. However, it does not disclose treating more than one target DNA in this manner. Therefore, claim 13 of Macevicz *et al.* does not disclose the step of annealing the oligonucleotide probe in the presence of a ligase, not does it disclose contacting a "DNA population" with an oligonucleotide probe. Figures 1 to 4 of Macevicz *et al.* disclose that there is a step of "annealing/ligating". However, the description of Macevicz *et al.* discloses that hybridisation and ligation are distinct method steps.

The description teaches that annealing and ligating take place sequentially. Macevicz *et al.* does not disclose hybridisation in the presence of a ligase.

The Office Action appears to indicate that Example 1 of Macevicz *et al.* discloses recording the quantity of each label. This passage discloses that the identity of the extended nucleotide is determined by "illuminating each reaction mixture with standard wavelengths". This passage does not disclose that the quantity of each label is recorded. Therefore, Macevicz *et al.* do not disclose the subject matter of part (e) of claim 21.

Macevicz *et al.* do not disclose all the features of claim 21. It does not disclose sequencing of multiple templates (each of which are present in a unique amount), hybridisation in the presence of a ligase, nor recording the quantity of each label cleaved from the ligated probes. Thus, the claims of the present invention are novel over the disclosure of Macevicz *et al.*

Therefore, Applicants respectfully request the withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 103

Claims 21-39 and 41-43 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* (WO 95/04160).

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art

> that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re* Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited reference does not teach or suggest that the claimed invention could be used with a reasonable expectation of success.

The Office Action asserts that claims 21-39 and 41-43 are obvious over the disclosures of Southern *et al.* and the Stratagene Catalog. Although the Office Action has rejected all pending claims, the comments of the Office Action only relate to the present kit claims. However, in the interest of expediting prosecution and without ceding to the rejection, Applicants address the rejection as it applies to all pending claims.

Southern *et al.* do not disclose sequencing multiple DNA templates simultaneously, without spatially resolving the templates (see also the discussion of Southern et al. as pertaining to the rejection under 35 U.S.C. § 102 above). Again, Applicants submit that the skilled artisan, based on what is disclosed in the specification and known in the art, would give the words "reaction" and "zone" their common meaning and understand that a reaction zone refers to a container or region where the templates are located in which the sequencing reaction takes

place. The present specification states "the invention provides a method for analysing heterogenous sub-populations of nucleic acids without spatially resolving them" [emphasis added]. The phrase "without spatially resolving them",indicates that the templates are present in the same container or region and are sequenced without the need for separation. In contrast, Southern *et al.* disclose sequencing multiple templates. Therefore, there would be no motivation to the skilled artisan for providing a kit comprising a means for resolving a measured quantity of the hybridized probe into quantities which correspond to unique amounts of the templates to which the probe hybridizes.

Therefore, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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